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The influence of breathing carbon monoxide and oxygen at high percentages for prolonged periods of time upon development of tar cancer in mice
Campbell, J. Argyll
J. Path. Bact. (1933), 36, 243-8

Cancer chemotherapy. XI. The effect of carbon monoxide, hydrocyanic acid and pituitrin upon tumor growth
Maxwell, L. C.; Bischoff, Fritz; Ullmann, Henry. Jr.
J. Pharmacol. (1933), 49, 270-82

Cancer of skin and increase in incidence of primary tumors of lung in mice exposed to dust obtained from tarred roads
Campbell, J. A.
British Journal of Experimental Pathology, Vol. 15, No. 5, pg. 287-294 (October 1934).

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THE INFLUENCES OF BREATHING CARBON MONOXIDE AND OXYGEN AT HIGH PERCENTAGES FOR PROLONGED PERIODS UPON DEVELOPMENT OF TAR CANCER IN MICE.

J. ARGYLL CAMPBELL.

From the National Institute for Medical Research, Hampstead.

AT the present time carbon monoxide occurs in the atmospheric air to a greater extent than formerly since it escapes from every motor exhaust pipe and is present in coal gas which is so widely used both for heating and for cooking purposes. There has been apparently an increase in incidence of lung cancer during recent years and it is of importance to eliminate any reasonable factor which may have a similar time relationship. Carbon monoxide is such a factor and I found recently (this *Journal*, 1932, xxxv. 379) that it had a retarding effect upon the growth of mouse carcinoma 63 while it had no effect upon rate of growth of the Rous fowl sarcoma. Since tar cancer in its development is perhaps like spontaneous cancer it was considered that experiments with carbon monoxide to determine its effect upon tar cancer would be more to the point than the above experiments with transplanted tumours. Therefore mice breathing carbon monoxide were painted with tar as were control mice breathing ordinary air, while a third series of mice breathing oxygen at about 60 per cent. of an atmosphere were similarly painted.

Technique.

Amsterdam tar was used, applications being made twice a week (Monday and Friday, or Tuesday and Thursday) for about 9 months, to a small area of skin in the middle of the back of the animal and the tar rubbed in gently for a few seconds. We purposely continued the tar applications throughout instead of stopping after about 3 months, as is often done, because at one period of the experiment the development of tar warts was much slowed down in the carbon monoxide series of mice and we were interested to determine whether the poisonous gas would counteract continuous tar application.

The carbon monoxide series of mice was enclosed in a respiratory chamber of about 280 litres capacity, the carbon dioxide produced by the mice being absorbed by soda lime spread out in trays and the oxygen consumed being automatically replaced from a gasometer. The air in the chamber was kept well mixed by means of a large fan propelled by a motor fixed in position outside the chamber. The mice were gradually acclimatised to the carbon monoxide, so that on the

1st, 5th, 10th, 20th, 24th, 27th, 39th and 46th days the percentages of carbon monoxide in the air breathed were 0·04, 0·06, 0·09, 0·10, 0·13, 0·17, 0·19 and 0·24 respectively. From the 46th day till the 269th day or end of the experiment the carbon monoxide was maintained at 0·24 per cent., and the surviving mice were evidently acclimatised to this amount as their body weights were as well maintained as were those of the other two groups. An accurately measured volume of pure carbon monoxide was added to the air in the chamber to obtain the required percentage. The breathing of the poison was continued for about 9 months which represents about one-third or one-fourth of a mouse's life and thus might be compared with 15 or 20 years of human life.

The food for the mice consisted of a mixture of wheat barley and oats in equal proportions and a little clean fresh green stuff. Sufficient food water and bedding were placed in the chamber to last about 3 or 4 days, so that the chamber had to be opened only twice a week for about 30 minutes to renew food, etc., and also to weigh the mice and paint them with tar. The animals were separated in groups of from 5 to 8 in boxes of the usual standard pattern with freely perforated lids.

The mice exposed to high oxygen pressure were enclosed in a similar chamber containing about 60 per cent. of oxygen in the gas mixture to be breathed, while the control mice breathing normal air were treated in exactly the same way as regards tarring, food, water, bedding, etc.

Effects upon general health.

At the start of the experiment, the carbon monoxide series of mice were, on an average, somewhat heavier than were the other two groups

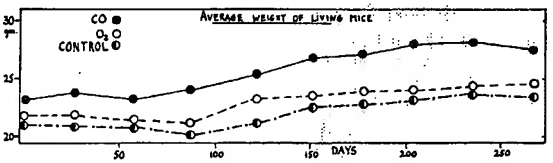


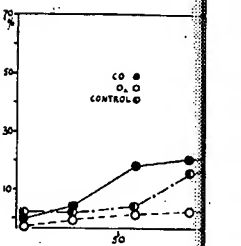
FIG. 1.

(fig. 1) and the surviving mice of the former group maintained this advantage throughout the experiment thus proving that these survivors were able to acclimatise themselves to the poison; some attempts to make them breed however failed, although some mice of the other two groups did breed. It will be observed that the weight curves were more or less parallel and that after the 90th day (17th March 1932) there was an obvious increase in average weight of each group, the increase affecting all the mice irrespective of any special experimental condition so that the cause was some general factor such as some improvement in diet, *e.g.* better quality of green stuff or the mice may have become more acclimatised to the tar painting and its effects.

There were more deaths amongst the carbon monoxide group than amongst the other two groups, as might be expected under the influence

of the poisonous gas (see fi
mice appeared to be more
two groups since in the fo

Day.	
0 (18.12.31)	.
27 (14.1.32)	.
59 (15.2.32)	.
87 (14.3.32)	.
122 (18.4.32)	.
151 (17.5.32)	.
178 (13.6.32)	.
208 (11.7.32)	.
235 (9.8.32)	.
269 (12.9.32)	.



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On the 122nd day in each
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of the poisonous gas (see fig. 2 and table I). The high oxygen group of mice appeared to be more resistant to the tar painting than the other two groups since in the former group by the 120th day there were only

TABLE I.

Number of animals alive.

Day.	Control.	CO.	High O_2.
0 (18.12.31) . .	51	50	49
27 (14.1.32) . .	51	48	43
59 (15.2.32) . .	49	41	48
87 (14.3.32) . .	43	40	48
122 (18.4.32) . .	41	38	47
151 (17.5.32) . .	41	36	41
178 (13.6.32) . .	39	34	38
206 (11.7.32) . .	36	27	38
235 (9.8.32) . .	34	23	37
269 (12.9.32) . .	29	19	32

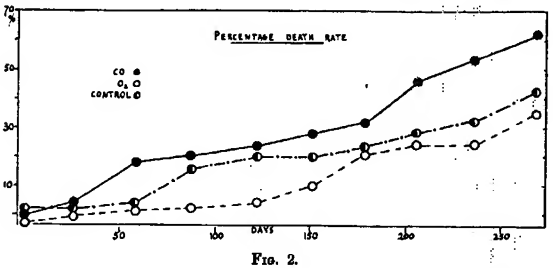

FIG. 2.

2 deaths whilst there were 10 and 12 deaths in the control and carbon monoxide series respectively. Fig. 2 which gives the percentages of mice dying in each group demonstrates that from about the 120th day onwards all the groups of mice showed an increase in death rate probably because the tar cancer now exerted its influence and bacterial infection was a factor since in some mice the skin had become broken at the cancer site.

Development of tar warts.

Tar warts were recorded as soon as they could be seen as minute specks, which occurred about the 12th week of tarring (table II). On the 122nd day in each of the three groups of mice there were 5 mice with small warts but on the 151st day there were 8, 14 and 19 in the carbon monoxide group, the controls and the high oxygen group respectively. In the carbon monoxide group on the whole there was a retardation in the appearance and development of the warts compared with the other two groups. In table II the number of living and dead

TABLE II.

Number of living and dead animals with warts, starting from the 108th day.

Day.	Controls.		CO.		High O_2.	
	Living.	Dead.	Living.	Dead.	Living.	Dead.
108	1	0	3	0	0	0
122	5	0	5	0	5	0
151	14	0	8	0	18	1
178	22	0	15	1	26	1
206	29	1	13	3	33	1
251	30	7	18	3	36	2
269	29	9	19	7	32	7

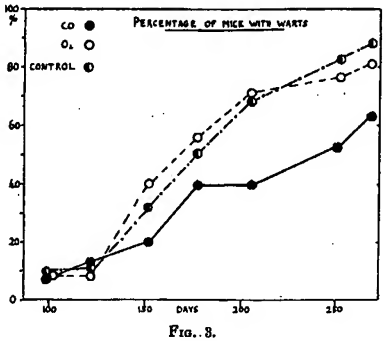

FIG. 3.

animals with tar warts is shown and in fig. 3 these two wart groups have been combined, the percentage of mice with warts being plotted against the time. The curve for the carbon monoxide group lies below those for the other mice. As seen from tables I and II, at the end of the experiment all the mice still living in each group had tar warts but the warts in the carbon monoxide group were not so well developed as were those in the other groups. It is concluded that the carbon monoxide retarded but did not prevent development of tar warts.

Development of tar cancer.

It is possible to obtain an approximate idea as to development of tar cancer in the skin of living mice by careful examination with the fingers and sense of touch. In this way it was noted by Dr Cramer, who kindly examined the mice towards the end of the experiment, that carbon monoxide definitely retarded the development of tar cancer compared with the control and high oxygen series of mice. At the end of the experiment all the mice were killed, and the tarred area of the

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Group.	Number with ca carci
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The general conditions
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*Conditions of lungs and li
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Group.	Total number of mice.
Controls. .	29 (100 per cent.)
CO. . .	19 (100 per cent.)
High O_2. .	32 (100 per cent.)

skin was bisected and examined histologically. The conditions of tar carcinoma as revealed by the microscope are shown roughly in table III, the evidence again being in favour of some retardation of cancer development by carbon monoxide. Special attention was paid to the arrangement of cancer cells and fibrous tissue but there did not appear to be any difference between the three groups of mice in these respects. The only special feature of the carbon monoxide group was the greater tendency to vascular congestion due probably to increase of erythrocytes.

TABLE III.

Tar carcinoma as revealed by microscope.

Group.	Number of mice with extensive carcinoma.	Number of mice with slight carcinoma.	Number of mice with no carcinoma.	Total.
Controls . . .	23 (79 per cent.)	4 (14 per cent.)	2 (7 per cent.)	29 (100 per cent.)
CO	8 (42 per cent.)	6 (32 per cent.)	5 (26 per cent.)	19 (100 per cent.)
High O_2 . . .	24 (75 per cent.)	4 (12 per cent.)	4 (13 per cent.)	32 (100 per cent.)

The area of scar tissue which often overlies the cancer area in such cases was measured in the different groups and as examined in this way the carbon monoxide group again revealed some retardation of development of pathological condition.

Conditions of the heart liver and lungs.

In the carbon monoxide group the organs revealed congestion and also the average weight of the hearts was greater in this group than that of either of the other series of mice, indicating an hypertrophy of the heart probably due to increase in viscosity of the blood following increase in red corpuscles as has been recorded elsewhere (*J. Physiol.*, 1932, lxxvii. 9 P).

The general conditions of the liver and lungs as regards metastases and infection (inflammatory reaction including pneumonia) due to entrance of bacteria etc., are demonstrated roughly in table IV.

TABLE IV.

Conditions of lungs and liver at end of experiment; number of mice with metastases and inflammatory reaction.

Group.	Total number of mice.	Lung.		Liver.	
		Metastases.	Inflammatory reaction.	Metastases.	Inflammatory reaction.
Controls .	29 (100 per cent.)	3 (10 per cent.)	12 (41 per cent.)	0	7 (24 per cent.)
CO . . .	19 (100 per cent.)	2 (10 per cent.)	5 (26 per cent.)	0	4 (21 per cent.)
High O_2 .	32 (100 per cent.)	3 (9 per cent.)	8 (25 per cent.)	0	6 (19 per cent.)

It is not always easy to determine in an inflammatory reaction whether the change is due to infection or to commencing malignancy. There were no striking differences between the three groups of mice except that in the controls the lungs more frequently revealed inflammatory reaction than in the other two groups.

Summary.

It is shown that carbon monoxide breathed for prolonged periods (one-third of life) retards, but does not prevent, development of tar cancer in mice. There is no evidence herein in favour of the hypothesis that the recently reported increase in human cancer is connected with the presence of carbon monoxide in the air of streets, garages, factories, kitchens, etc.

Breathing oxygen at 60 per cent. of an atmosphere has no effect upon development of tar cancer in mice.

I am indebted to my assistant, Mr C. Pergande, for much help in this research.

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